

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
TETRACHLORVINPHOS

Chemical Code # 305, Tolerance # 252
SB 950 # 117

April 4, 1986

Revised 8/11/86; 1/22/87; 7/14/87; 5/25/88; 9/6/90, 2/4/91, 1/17/96, 7/11/96, and 3/12/97

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect ^H
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, possible adverse effect
Neurotoxicity:	No data gap, no adverse effect

^H An additional study (HLA Study No. 10913-0-401R) was submitted to U.S. EPA, but has not been received at DPR as of 3/11/97. U.S. EPA considered the study acceptable and negative, however this report should be submitted to DPR for independent review. Aldous, 3/11/97.

Toxicology one-liners are attached.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T970312

Revised by: J. Gee, 2/4/91; C. Aldous, 1/17/96, 7/11/96, and 3/12/97

These pages contain summaries only. Individual worksheets may identify additional effects.

All relevant records through Record No. 151705 (in Document No. 252-084) have been reviewed. This includes all records indexed with DPR as of 3/11/97. Some records of an older record number series (> 900000) are also found in this Summary. Aldous, 3/11/97.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED CHRONIC/ONCOGENICITY, RAT

****252-065 125082** Mulhern, M., D. Robb, C.J. Perry, P. Millar, C. Atkinson, "Tetrachlorvinphos: 104 week dietary combined chronic toxicity/carcinogenicity study in rats", Inveresk Research International, 7/29/93. IRI Project No. 438403. Tetrachlorvinphos, purity 99%, was administered in diet at 0, 100, 1000 or 2000 ppm to 50 Sprague Dawley rats/sex/group for 104 weeks. An interim sacrifice group of 15 additional rats/sex/group were sacrificed at week 52. NOEL = 100 ppm (hypertrophy of periportal hepatocytes, diffuse lipidosis of adrenal zona fasciculata, hepatocytic centrilobular degenerative changes (males only), moderate body weight decrements (females only), and plasma cholinesterase (and to a lesser extent RBC cholinesterase) inhibition (primarily in females). A **"possible adverse effect"** is an equivocal effect on histiocytic sarcoma incidence in high dose males (incidences of 0, 1, 2, and 5 in controls through high dose males, respectively). **Acceptable.** Kishiyama and Aldous, 1/17/96.

NOTE: See comments under "Oncogenicity, Rat", below.

252-057 117975 Interim report to Record No. 125082, above. No DPR review is needed, since the final study is available.

CHRONIC TOXICITY, RAT

033 038775, "Oral Toxicity of the Halophenyl Vinyl Phosphate Insecticide Gardona (SD 8447): Two Year Oral Experiment in Rats", (Shell Toxicology Lab, England, 11/67); Tetrachlorvinphos (95+%); Final report of 28967. Twenty-five per sex per group were given 0, 5, 25, 125 and 2000 ppm in the diet over two years. Test article at 95% purity. At the high dose, moderate decrease in body weight gain, decrease in food consumption, cholinesterase inhibition in plasma and erythrocytes were reported. No adverse effect reported. NOEL: 125 ppm for cholinesterase inhibition and decreased weight gain. UNACCEPTABLE - Not upgradeable: no individual clinical observations, no summarization of gross and histopathology findings, no urinalysis, only a single analysis of diet over two years, inadequate number of animals per group (but survival resulted in a reasonable number alive at 104 weeks), and dose selection was not justified. (J. Remsen, 4/1/86)

015 028967, (1966, Tunstall), Interim report, see 38775. (Apostolou, 6/4/85).

015 936843, Summary of data presented in 28967 (no worksheet).

020 936836, Brief overview of many studies (no worksheet).

SUBCHRONIC, RAT

****252-083 147801** Perry, C.J., M. Mulhern, W. Henderson, and P. Hudson, "Tetrachlorvinphos: 13 week dietary toxicity study in rats", Inveresk Research International, Tranent, Scotland, Jan. 11, 1990. IRI Project No. 438141. Ten Sprague-Dawley rats/sex/group were dosed with 0, 100, 2000,

or 5000 ppm tetrachlorvinphos (99% purity) in a guideline subchronic study design. NOEL = 100 ppm [plasma and RBC cholinesterase inhibition in both sexes; primary histopathology changes were liver centrilobular hypertrophy (both sexes) and generalized cellular enlargement (males), basophilic tubules in kidneys of males, adrenal cortical cellular alteration (females), and thyroid follicular cell hypertrophy (both sexes)]. No adverse effects. Aldous, July 8, 1996.

252-046 091037 Summary of the 13-wk study above, examined by Chernoff, 7/4/90 (no worksheet).

CHRONIC TOXICITY, DOG

NOTE: The 1993 study below explored a much higher dosage range than did the unacceptable study completed in 1968. The later study did not confirm the histopathological effects reported in the earlier study. The overall assessment is that there are no adverse effects indicated for chronic dog studies. Aldous, 1/4/96.

****252-061 120978** Tompkins, E.C., "One year oral (capsule) toxicity study in dogs with Rabon", WIL Research Laboratories, Inc., 1/28/93. Lab Study No. WIL-149009. Tetrachlorvinphos technical (trade name = Rabon), 99% purity, was administered via gelatin capsules at 0, 6.25, 500 or 1000 mg/kg/day to four beagle dogs/sex/group for 1 yr. NOEL (other than for cholinesterase inhibition) = 6.25 mg/kg/day [increased liver and kidney weights in both sexes: hematology changes, particularly decreased RBC counts, decreased Hb, and increased MCV in both sexes: modest increase in alkaline phosphatase levels in both sexes: decreased urine specific gravity in males]. Plasma cholinesterase inhibition was marked in both sexes at 500 to 1000 mg/kg/day, and equivocal in 6.25 mg/kg/day males. There was no effect on brain or RBC cholinesterase at any dose level. **Acceptable. No adverse effects.** Kishiyama and Aldous, Jan. 3, 1996.

035 038799, "Two-Year Dietary Administration of SD 8447 (Tetrachlorvinphos) to Dogs", (Hill Top Research, Miamiville, OH, 5/68). Three/sex/group were fed 5, 25, 125, and 2000 ppm. Another group of three/sex was started some months later at 200 ppm to investigate cholinesterase inhibition. UNACCEPTABLE - Not upgradeable - no justification for dose selection, no diet analysis, test article not described, inadequate number of animals, limited histopathology on low- and mid-dose animals. Depression of plasma cholinesterase is the only indication that high dose may be approaching an adequate dose (50-60% of control). **Positive for adverse effect on kidneys of females** -- alteration in the morphology of epithelium with vacuolization in 3/3 at 2000 and 3/3 at 200 ppm and 1/3 at 125 ppm. No loss of function was reported. (J. Remsen, 4/3/86).

ONCOGENICITY, RAT

(see accepted rat combined dietary study, above)

030/033 936890, "Bioassay of Tetrachlorvinphos for Possible Carcinogenicity - Rat", (1978, Gulf South Res. Inst./NCI). Fifty per sex per group were fed 8000/4000 and 16,000/8000 (technical grade) for 80 weeks, then observed for 31 additional weeks. **Adverse effect:** Oncogenicity (C-cell adenoma of thyroid in females, C-cell hyperplasia in male and female; cortical adenoma of adrenal in females). UNACCEPTABLE - Not upgradeable; No individual data. Two doses only with changes in levels at 5 weeks. Only ten per sex as vehicle controls. (A. Apostolou, 6/3/85)

252-030 936890 This is a re-examination of a previously submitted document entitled "Bioassay of tetrachlorvinphos for possible carcinogenicity", NCI Technical Report Series No. 33. In-life phase was at Gulf South Research Institute, dated 1978. Re-examination was needed because a

1993 rat combined study has been accepted (Record No. 125082). This examination confirms that dose levels of 4000 to 8000 ppm in Record No. 936890 were excessive for female rats. Comparison of the two studies does not negate the likelihood that adrenal cortical tumors or thyroid C-cell tumors were treatment effects, however effects were only attained above the MTD. The lack of evidence in this study for a treatment effect on histiocytic sarcoma incidence does not alter the conclusion of a possible treatment effect in the 1993 study (see review of Record No. 125082), so the data requested in the review of that study are still relevant. Aldous, 1/8/96.

033 038776, (1977, Shell). Supplement to 030 936890. A critique of the GSRI study (J. Remsen 4/1/86).

033 038777, 1977 Critique of bioassay (rats), 936890

ONCOGENICITY, MOUSE

****[no new record or document number]** This is a re-examination of several records relating to the same study, originally presented as the unpublished report (Hazleton Project No. 776-118, dated 6/20/80, submitted to CDFA as Document No. 252-034, Record No. 038790, under the tab "Addendum 9, Vol. 2"). In the same record, under the tab "Addendum 9, Vol. 1" is a Shell Development Company analysis of the same study, which included a re-evaluation of kidney and liver pathology by a consultant pathologist. Several records in Document Nos. 252-034 and 252-040 contain individual data or commentaries on the same study. Document No. 252-037, Record No. 051634, contains a published report of this study, incorporating re-evaluation by the consultant pathologist. Study design and conduct has been previously evaluated, and the study has been classified as **acceptable**. The re-review does not change this study status. The study should still be considered to indicate a "possible adverse effect", based on kidney tumors and liver nodules. The liver nodules were considered by the study pathologist to be hepatocellular carcinomas. The case was made by a consultant pathologist, although not verified by a peer review panel as recommended by current U.S. EPA guidelines, that treatment caused an increase in non-neoplastic nodules, but not in neoplasia. The current review does not resolve the issue regarding possible neoplastic nature of liver nodules, but instead acknowledges both interpretations. Doses at or above 8000 ppm are clearly in excess of an MTD, suggesting that these study results may have little value in evaluating tumor risks to humans. There are no definitive treatment effects at or below 1600 ppm, suggesting that dose as a NOAEL. Aldous, 1/17/96 (please see worksheet W038790.S01).

**** 034, 040 038790-93, 038797-98, 057712**, "Lifetime Oncogenicity Oral Feeding Study of SD-8447 in B6C3F1 Mice". Original Hazleton Laboratories America, Inc. report dated 7/80 and 1987 (compilation of individual data in Document No. 252-040). The publication in Fundam. Appl. Toxicol. (see Document No. 252-037, below) covers the same study. Tetrachlorvinphos, lot 12-TMJ-169, 98.7% (current production technical, was used for all groups except for the second replicate at 16000 ppm) and Lot 05MMJ241, 98.7% [the lot used in the 1978 NCI study (Document No. 252-030, below)], was used for the second replicate at 16000 ppm. Mice were dosed by diet for two years at 0, 17.5, 64, 320, 1600, 8000 or 16,000 ppm. There were 160/sex in control group and 80/sex in treatment groups (with 20/sex/control group or 10/sex/treated group sacrificed at 6, 12 and 18 months). Study was performed because of problems in the 1978 NCI study (see below). The Hazleton study pathologist concluded that a.i. elicited hepatocellular carcinomas at or above 8000 ppm in females, and at 16000 ppm in males, as well as renal tubular carcinomas in 16000 ppm males. A consultant, Dr. Vesselinovitch, reviewed the slides. He found no increase in hepatocellular neoplasia, however he found an increase in "adenomatoid and hyperplastic nodules" in livers. He agreed with the study pathologist on the significant increase in renal tubular

tumors, but judged most of these as adenomas. All notable findings were at 8000 and 16000 ppm, at which doses animals showed severely depressed body weights; increased liver weights; various pathological changes in kidneys, adrenals, reproductive tissues, and especially the liver; sharply increased survival; and other evidences that these dose levels greatly exceeded the MTD. Systemic NOEL = 1600 ppm [body weight depression, liver nodules (disputed as to whether neoplastic), kidney tumors, and major liver pathology]. Initially reviewed as unacceptable but upgradeable (J. Remsen, 4/2/86) due to lack of individual body weights and clinical observations. Submission of # 057712, individual data, upgraded the study to ACCEPTABLE status with a possible adverse effect on liver and kidney. Gee, 4/2/86 and 5/24/88. Updated by Aldous, 1/17/96.

****252-037 051634** Parker, C. M. et al., "Lifetime Oncogenicity Oral Feeding Study of SD-8447 in B6C3F1 Mice", Hazleton Laboratories America, Inc. Report is a publication in Fundam. Appl. Toxicol. 5, 840-854 (1985). This is the same study presented in the unpublished reports above (see Document Nos. 252-034 and 252-040, Record Nos. 038790-93, 038797-98, and 057712). A CDFA review was prepared for this record by J. Remsen (Gee) on 1/22/87.

252-030 038283 [The report on rat and mouse oncogenicity was originally designated by Record No. 936890. Record No. 038283 was later applied to the mouse segment of the study, whereas Record No. 936890 was retained for the rat segment.] "Bioassay of Tetrachlorvinphos for Possible Carcinogenicity" - Mice (1978, Gulf South Research Inst./NCI). Two doses were used: 8000 and 16,000 ppm technical. tetrachlorvinphos, (98-99.5% purity) in the diet for 80 weeks, followed by 12 weeks of observation. Ten per sex were concurrent controls with 50/sex/group in treated groups. As stated in 038776 and 038780, the study had serious problems including interpretation of the slides. The pooling of controls from other studies but not those in the same animal room is not explained. In addition, those two studies were on malathion and dieldrin, both of which could alter the animal response to organophosphates. If cross contamination of materials occurred, the study might be seriously compromised. See subsequent testing by Shell Development Co. (Record No. 038790 and related documents) for a repeat mouse oncogenicity study. Critique 038776 also raises the issue of the strain of mice actually used as there is a discrepancy in information from the supplier with the dates in the report. UNACCEPTABLE - Not upgradeable with a **positive finding for oncogenicity**. Hepatocellular carcinoma incidence in males was reported as 5/49, 36/50, and 40/50 for pooled controls through high dose groups, respectively; corresponding incidences in females were 0/9, 5/49, and 2/47. Neoplastic nodule incidence in males was 0/9, 11/50, and 2/50, respectively, with corresponding incidence in females reported to be 1/48, 14/49, and 9/47 for pooled controls through high dose groups, respectively. Virtually all treated mice had granulomatous inflammation, compared to none of the controls of either sex. All treated groups displayed body weight decrements: degree was clearly excessive for both treated female groups and for high dose male mice, and marginally excessive for 8000 ppm males. (A. Apostolou, 6/3/85) (clarifications by Aldous, 1/8/96).

252-033 038789 A Sept. 1977 version of 252-030:038283, above.

033 038776, Critique (by sponsor) of the above NCI study, citing weaknesses in both rat and mouse data. A brief evaluation by the consultant pathologist, Dr. Vesselinovitch, questioning mouse liver tumor evaluation, is included.

252-033 038780 An analysis by consultant pathologist, Dr. Vesselinovitch, on liver nodules in the above NCI study. He concluded that the incidences of benign lesions (particularly hyperplastic nodules) was elevated in both treated groups. Incidences of trabecular tumors (synonymous with hepatocellular carcinomas) were 0/9, 8/50, and 9/50 in concurrent controls, 8000 ppm, and 16,000 ppm groups, respectively. By adding in historical control data, he achieved control incidence of

3/48, which rendered the incidences in the two treated groups **not** statistically significant. Aldous, 1/17/96 (no worksheet).

033 038781, This record contains various letters, including one from Dr. Paul Neuberne, regarding his own (admittedly conservative) diagnostic criteria for liver lesions. The letter does not state whether or not he was in general agreement with Dr. Vesselinovitch. Nevertheless, Dr. Neuberne stated that the "the table listing various diagnosis by Stanley [Vesselinovitch], myself, and the Gulf South pathologist appear to reflect accurately my assessment of the slides I looked at". A page in this same record shows a table of diagnoses, in which Neuberne and Vesselinovitch had comparable diagnoses on a series of specimens, each finding 4/9 to 5/9 carcinomas, compared to 9/9 diagnosed as carcinomas by the Gulf South pathologist. Aldous, 1/17/96 (no worksheet).

033 038779, 1978 lesion analysis on C57BL X C3H F1 mice.

REPRODUCTION, RAT

****252-055 098288** Barton, S.J., "Tetrachlorvinphos two generation reproduction study in rats", Inveresk Research International, 8/28/91. IRI Project No. 438712. Tetrachlorvinphos (trade name "Rabon"), 99% purity, was administered in diet at 0, 100, 500 or 2000 ppm to CD CrI:(SD) BR rats (28/sex/group for F0 rats and 24/sex/group for F1 rats). Parental NOEL = 100 ppm (adrenal cortical hypertrophy in F1 females only). Also, body weight gain was reduced in 2000 ppm F1 parents. Developmental NOEL = 2000 ppm (no developmental toxicity). Study was classified as unacceptable, but upgradeable in the original DPR review (histopathology of parental rats was necessary). Requested data were supplied in Document # 252-084, Record # 151705. New data lowered the parental toxicity NOEL, nevertheless there are **no adverse effects**. The study is now **acceptable**. Kishiyama and Aldous, 12/13/95; Aldous, 3/11/97.

034 038800, "Results of Reproduction Study of Rats Fed Diets Containing SD 8447 (Tetrachlorvinphos) Insecticide Over Three Generations", (Hine Lab., S. F. 9/66). More complete version of 936895. Ten males and 20 females were fed 100, 333 and 1000 ppm in a three-generation study, two litters per generation. No parental gross necropsy. Histopathology on 10 per sex selected from the F3b litters. The initial review (A. Apostolou 6/4/85) of this study identified a possible adverse reproduction effect. Re-evaluation of the more complete report with additional data finds no adverse effect. The only finding as in the initial review was increased liver weights in male pups. This is not considered a reproductive effect and the liver has been identified as a potential target organ for chronic/oncogenicity effects in other studies in the package. UNACCEPTABLE due to missing information on test article, diet analysis, no justification of doses, individual data not included, other faults. (J. Remsen 4/3/86)

015 936895, (1966, Hine Labs); Apostolou, 6/4/85. See 038800.

015 038265, Summary of study in 936895.

015 936843, Summary of study in 936895.

024 936861, Summary of study in 936895.

TERATOLOGY, RAT

** 039 056945, "A Teratology Study in Rats with T-142-4 Technical Rabon", (Argus Research Lab, PA, 4/1/87, 1019-003). Tetrachlorvinphos technical (98.6%) given by oral gavage to 25 per group at 0, 75, 150 or 300 mg/kg/day, days 6 - 15 of gestation in 2 trials. Trial 1 was terminated due to low fertility in all groups due to males. In trial 2, there were no deaths or abortions; clinical signs consisted of chromodacryorrhea, urine-stained abdomens, chromorhinorrhea and tremors in the high dose group. Body weight gain was decreased in the high dose group by 6 - 9% during dosing and marginally in mid-dose group, especially early in dosing period. Maternal NOEL = 75 mg/kg (decreased weight gain, clinical signs at 300 mg/kg); developmental NOEL \geq 300 mg/kg. No adverse effect on development of fetuses. Initially reviewed as unacceptable (M. Harnois, 7/21/87) but upgradeable with submission of a legible copy of historical control data. These were submitted 12/7/87. Study is upgraded to ACCEPTABLE status. (Gee, 5/24/88)

041 064269, "A Teratology Dose Range-Finding Study in Rats with T-142-4", (Argus, 11/17/87, 1123-85-0073-TX-003). Tetrachlorvinphos, lot 10-56-0-0, white powder, 98.6%; given by oral gavage to groups of 8 Sprague-Dawley Crl:COBS CD rats in two phases with doses of 0 (0.5% methyl cellulose), 50, 100, 500 or 1000 mg/kg/day and 0, 200 or 300 mg/kg/day (phase 2), gestation days 6 - 15; analysis of dosing solutions showed stability for 7 days (Appendix B); 4/8 at 500 and 7/8 at 1000 mg/kg died (1 at 500 due to dosing error); clinical signs at 300, 500 and 1000 mg/kg were tremors, decreased motor activity, hyperreactivity, salivation, chromodacryorrhea, chromorhinorrhea and others; loss of body weight and/or decreased gain at 300, 500 and 1000 mg/kg (marginal but statistically significant effect at 200 mg/kg) with decreased food consumption early in dosing period; fetal weight slightly lower at two highest doses but no effect on resorptions; maternal NOEL = 100 mg/kg/day, developmental NOEL \geq 1000 mg/kg/day; supplemental to CDFA (now DPR) # 056945. (Gee, 5/26/88)

TERATOLOGY, RABBIT

** 027 936891-3, "Teratology Study in Rabbits with DS-36779 (Rabon Technical)", (WIL Research Lab., Cincinnati, OH, 10/82). Eighteen per group were given 0, 150, 375 and 750 mg/kg/day by oral gavage on days 6-19. NOEL (maternal): 375 for body weight. NOEL (developmental): 375 for slight increase in resorptions. with no adverse effect identified. ACCEPTABLE (A. Apostolou, 6/3/85)

034 038801, Exact duplicate of 936891

GENE MUTATION

** 033 038769, "Toxicity Studies with Gardona: Mutagenicity Studies in Micro-organisms In Vitro (Salmonella typhimurium and Escherichia coli)", (Shell, 1978). Salmonella strains TA1535, TA1538, TA98 and TA100 were tested with and without rat and mouse liver activation at 0, 0.2, 2, 20, 500 and 2000 μ g/plate (99.3%). Both induced and non-induced livers were used. In addition, E. coli WP2 and WP2 uvr were included. Although TA1537 was not included in this study, all results are negative for the other strains and E. coli as well. At 2000, TA100 colony counts are somewhat lower suggesting a cytotoxic effect; no adverse mutagenic effect reported. Multiple trials. ACCEPTABLE. (J. Remsen 3/31/86).

157-009, 034551, "The Mutagenic Effect of Organophosphate Insecticides on Escherichia coli", (Shell, Tunstall, TLGT0034.71, 8/71). Gardona (greater than 99% pure; ex WARC., TSL 8/69/B) was tested in the spot test (no concentration. given) in E. coli WP2; No toxicity or increase in

revertants reported. Insufficient information for assessment of adverse effect. UNACCEPTABLE: summary report only. No worksheet. (Harnois, 7/14/87)

252-049 089307 Lawlor, T. E. and D.C. Valentine, "Mutagenicity test on tetrachlorvinphos (TCVP): Rabon in the Ames Salmonella/microsome reverse mutation assay". This is the U.S. EPA data review worksheet by Byron Backus, indicating a negative and acceptable study. This study, performed at Hazleton (HLA Study No. 10913-0-401R) was not listed in the DPR printout of 12/14/95. The report should be submitted to DPR for independent review. Aldous, 1/4/96.

CHROMOSOME EFFECTS

033 038774, "Toxicity Studies with Gardona: Dominant Lethal Assay in Male Mice After Single Oral Doses or 5 Daily Oral Doses of Gardona", (Shell Toxicology Lab., England, 9/76). Twelve males per group (24 or 36 for negative controls) were given 0, 1000, 2000 and 3000 mg/kg or 200 and 400 mg/kg (Technical) by oral gavage. Males were mated 1:3 over 8 weekly periods with no dominant lethal effect. no adverse effect reported. UNACCEPTABLE - Not upgradeable. No individual data, dead animals not clearly identified, inadequate number of treated males per group, doses not justified, positive control (MMS) showed marginal effect. (J. Remsen, 4/1/86)

033 038773, "Toxicity Studies with Gardona: Chromosome Studies on Bone Marrow Cells of Chinese Hamsters After Two Daily Oral Doses of Gardona," (Shell Toxicology Lab., England, 11/74) In vivo cytogenetics in Chinese hamsters. Four per sex per treatment group were given 1000 and 2000 mg/kg (Technical) twice, and sacrificed at 8 or 24 hours. Cyclophosphamid as positive control. No adverse effect. UNACCEPTABLE, upgradeable. Dose selection should be justified. Individual data are missing. (J. Remsen 4/1/86)

**** 036 090586** "Mutagenicity Test on Tetrachlorvinphos (TCVP) in an In Vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells." (Murli, H., Hazleton Laboratories America, HLA 10913-0-437, 12/1/89) Chinese hamster ovary cells (CHO-WBL) were treated with technical tetrachlorvinphos. Without activation, concentrations used were 0 (medium and solvent controls), 29.9, 44.9, 59.9, 79.8 and 99.8 mg/ml for 17.25 hours with fixation at 20 hours. With activation with male Sprague-Dawley rat liver S9, concentrations were 0, 6.26, 12.5, 25, 27.6, 75.1, 113, 150 and 200 mg/ml, for 2 hours followed by an additional 8 hours with fixation at 10 hours. Schedule and concentrations were based on a range-finding study with incorporation of BrdUrd over 25 hours. There was an increase in the number of aberrations per cell and percent of cells with aberrations with concentration in the absence of activation. **Possible adverse effect.** No increase in aberrations were noted with activation. ACCEPTABLE. (Gee, 9/4/90 and 2/1/91) Rebuttal in 252-048.

DNA DAMAGE

033 038770, "Toxicity Studies With Gardona: Effect of Gardona on Micro-organisms in the Host-Mediated Assay and In Vitro (Saccharomyces cerevisiae and Serratia marcescens: Diploid Cells)," (Shell Toxicology Lab., England 11/74) Host-mediated assay & In vitro S. cerevisiae. Saccharomyces was exposed in vivo in male mice given oral doses to 2000 and 4000 mg/kg (98.8%) or in vitro to 0.2 and 0.4 mg/ml for 4 and 24 hours. No adverse effect reported. UNACCEPTABLE - Not upgradeable. Evidence that the test article reaches the yeast is not presented. The protocol for the in vitro test is not clear about plates/ concentrations selected. (J. Remsen 4/1/86)

033 038771-2, "Studies of the Effect of Gardona Upon the Integrity of Mouse Liver DNA In Vivo", (Shell Toxicology., Lab., England, 8/79). These two studies measured the effect of treatment of mice and rats on the DNA of liver as measured by alkaline sucrose gradients. Neither report indicates a change in molecular weight after treatment. (No worksheet.)

****45 090708** "Mutagenicity test on tetrachlorvinphos in the rat primary hepatocyte unscheduled DNA synthesis assay." (Cifone, M. A., Hazleton Laboratories America, HLA 10913-0-447, 12/1/89). Tetrachlorvinphos technical was tested with uninduced primary hepatocytes from a male Fischer 344 rat. The concentrations scored were 0 (DMSO), 0.503, 1.01, 2.52, 5.03, 10.1 and 25.2 mg/ml following 18.3 hours of treatment and a total of 22.6 hours incubation. Five replicates were assayed with 2 for toxicity. Net nuclear grains were determined by autoradiography of incorporated tritium-labeled thymidine as a measure of induced unscheduled DNA synthesis. At 25.2 mg/ml, the percent of cells with ≥ 6 net grains was significantly increased but the UDS grains/nucleus was not. Survival at 22.6 hours was 58.4%. There was no evidence of UDS at any other concentration. These results, without confirmation, are equivocal. Initially evaluated as unacceptable (needed individual data for evaluation of "equivocal" effect.) (Gee, 9/5/90) A second revision of the study was submitted (252-048, record 095828) containing the value for each of the 3 slides per concentration. The study was upgraded to ACCEPTABLE with a **possible adverse effect**. (Gee, 2/4/91)

048 095828 Second revision of 090708 dated 12/6/90.

252-049 089308 U.S. EPA review of the original report of Record No. 090708, above (concluding equivocal response in an unacceptable study). No DPR review is relevant (Aldous, 1/4/96).

NEUROTOXICITY

**** 047 088574** "Acute delayed neurotoxicity study in hens with Rabon technical." (Naas, D. J., WIL Research Laboratories, Inc., OH, WIL-149006, 6/27/90) Tetrachlorvinphos technical, 99%, lot 01-KMJ-012, was given by oral gavage at 0 (corn oil), 2500 or 5000 mg/kg with atropine sulfate protection to domestic hens. TOCP [TOTP] was the positive control. There were 6 hens in the negative and positive control groups and 15 in each of the test groups. The 2500 mg/kg group was re-dosed on day 21 and observed for an additional 21 days. In the 5000 mg/kg group, 11/15 died within 5 days of the initial dose. Clinical signs were observed after dosing at 2500 mg/kg but these disappeared by day 9. There was no evidence that tetrachlorvinphos caused acute delayed neurotoxicity although there were some neurological findings of a non-specific nature. ACCEPTABLE. (Gee, 9/6/90)

014/015 936915, "Demyelination Studies with the Insecticide SD 8447 (Fowl)," Shell Toxicology. Lab., 5/65). Twelve hens were dosed at 1.5 g/kg once or 300 mg/kg/day for 5 days. Insufficient information to evaluate but no adverse effect was identified. UNACCEPTABLE - Not upgradeable. Summary report with no details of histopathology, no individual animal data, no redosing at 21 days. (A. Apostolou, 6/3/85).

015 936843, Summary of study in 936915.

024 936861, Summary of study in 936915.

034 038802, Duplicate of 936915.